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Neonatal Neurologic Assessment Group; Kuiper, M J; Meiners, L C; Chandler, E S; Brandsma, R; Bos, A F; Horst, H J Ter; Sival, D A

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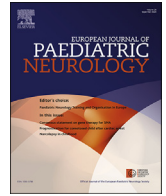
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Dyskinesia Impairment Scale scores in Dutch pre-school children after neonatal therapeutic hypothermia



M.J. Kuiper^a, L.C. Meiners^b, E.S. Chandler^a, R. Brandsma^a, A.F. Bos^c, HJ ter Horst^c,
D.A. Sival^{c,*}, Neonatal neurologic Assessment Group

^a Department of Neurology, University Medical Center Groningen, University of Groningen, the Netherlands

^b Department of Radiology, University Medical Center Groningen, University of Groningen, the Netherlands

^c Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, the Netherlands

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ABSTRACT

Background: Neonatal therapeutic hypothermia (TH) can ameliorate or prevent the development of dyskinetic cerebral palsy (CP) after hypoxic-ischemic encephalopathy (HIE). The Dyskinesia Impairment Scale (DIS) was recently launched to quantify dyskinetic (dystonic and choreatic) motor features in patients with CP. In TH treated children, who are at risk of developing dyskinetic CP, we aimed to determine DIS-scores at pre-school age.

Method: In 21 Dutch pre-school children (3–6 years of age) who had received TH according to the Dutch-Flemish treatment protocol, we determined DIS-scores. We associated DIS-scores with 1. age-matched control values (Kuiper et al., 2018) [1], and 2. previously reported DIS-score range in dyskinetic CP (Monbaliu E et al., 2015).

Results: The motor phenotype was determined as: normal ($n = 18/21$), mildly impaired (reduced coordination ($n = 2/21$)) and abnormal (dyskinetic CP; $n = 1/21$). In absence of CP ($n = 20/21$), DIS-scores were lower (more favorable) than in dyskinetic CP, without any overlapping group scores (mean difference: 71 points; $p < .05$). However, the obtained DIS-scores were still higher than previously reported in healthy age-matched controls (mean difference: 14 points; $p < .05$). There was an association between DIS-scores and retrospective neonatal MRI (basal ganglia and thalamus injury on diffusion weighted imaging (DWI)) and (a)EEG parameters ($p < .05$).

Conclusion: In the vast majority (95%) of Dutch TH-HIE treated pre-school children, the phenotypic motor outcome was favorable. However, DIS-scores were moderately increased compared with healthy age-matched controls. Future studies may elucidate the significance of moderately increased DIS-scores should to further extent.

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1. Introduction

Therapeutic neonatal hypothermia (TH) can effectively ameliorate or prevent neurologic damage in infants suffering from hypoxic-ischemic encephalopathy (HIE) [2–5]. The underlying mechanism of hypoxic ischemic damage can be divided into two phases. The primary phase induces immediate neuronal death and the secondary phase induces delayed neuronal damage, starting at 6 h after the insult, peaking at 24–48 h [6]. The secondary phase is characterized by accumulation of excitotoxic neurotransmitters (i.e. glutamate) [4,5], release of free radicals and pro-inflammatory cytokines providing a therapeutic time window for TH before apoptosis sets in [6,7]. The vascular border zones, the regions with a high metabolic demand, and the regions with a high density of

Abbreviations: DIS, Dyskinesia Impairment Scale; DIS-D, summed scores for dystonia; DIS-C, summed scores for choreoathetosis; TH-HIE, therapeutic hypothermia for hypoxic-ischemic encephalopathy; CP, cerebral palsy; DWI, diffusion weighted image; IR, Inversion recovery; MRI, magnetic resonance imaging; PLIC, posterior limb of the internal capsule; PWML, punctate white matter lesions; EEG, electroencephalogram; ICC, Intraclass Correlation Coefficient; PPV, positive predictive value; NPV, negative predictive value; DCD, developmental coordination disorder.

* Corresponding author. Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, PO Box 30001, 9700RB, Groningen, the Netherlands.

E-mail address: d.a.sival@umcg.nl (D.A. Sival).

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excitatory (glutamate) receptors are vulnerable to this type of damage [6]. This may result in damaged peri-rolandic and visual cortical areas, basal ganglia, thalamus, cerebellum and corticospinal tracts (e.g. posterior limb of the internal capsule (PLIC)) [6]. Consequently, the child may develop neurologic features including dyskinetic cerebral palsy (CP; i.e. combined dystonia, choreoathetosis and spasticity) [8], often with comorbid epilepsy, visual and/or cognitive- and behavioral impairment [8,9].

Monbaliu et al. have recently launched the Dyskinesia Impairment Scale (DIS) that enables quantification of the dyskinetic motor features in children with CP [9,10]. The total DIS-score consists of summed scores in dystonic and choreo-athetotic subscore domains (DIS-score = DIS-D + DIS-C subscale scores) [9,10]. For the interpretation of DIS-scores in young children, it is important to realize that healthy young children can also reveal mild “physiologic” dystonic and choreo-athetotic motor features that can meet the DIS scoring criteria [1]. These “false positive” scores are attributable to the uncompleted physiologic development of the central nervous system (CNS), including the shaping of the motor network [1]. It is therefore implicated that DIS-scores in young children, who are at risk of developing dyskinetic CP, should be interpreted against healthy, age-related control values [11,12]. Recently, we have published “physiologic” age-related DIS-scores in healthy children, that were obtained according to the official DIS score guidelines [1].

In a cohort of Dutch TH-HIE-treated pre-school children who are at risk of developing dyskinetic cerebral palsy, DIS-scores have not been obtained and interpreted against healthy age-matched control values, before. As successful neonatal TH-HIE treatment strategies may increasingly prevent or ameliorate the development of dyskinetic CP, we reasoned that insight in quantitative, age-related DIS-scores after TH-HIE treatment could provide useful information. In a cohort of Dutch TH-HIE-treated pre-school children who are at risk of developing dyskinetic cerebral palsy, we therefore aimed to determine DIS-scores and to interpret outcomes against previously reported scores in a. healthy age-matched controls [1] and b. dyskinetic CP (Monbaliu E et al., 2015).

2. Methods

The medical ethical committee of the University Medical Center Groningen (UMCG) the Netherlands, approved this observational study. Pediatric inclusion criteria were: pre-school children that had received TH-HIE in accordance with the Dutch-Flemish guidelines, see Appendix A (15); aged 3–6 years of life; included and treated at UMCG between 2009 and 2012; a traceable address for study invitation; signed informed consent form by the parents. Pediatric exclusion criteria were: chromosomal anomalies and any other syndrome or disorder (independent of perinatal asphyxia) that could possibly interfere with the execution of motor tasks.

Between 2009 and 2012, 48 asphyxiated neonates had received TH-HIE at UMCG, according to the Dutch guidelines for inclusion, see Appendix A [13]. Of the eligible children that fulfilled the inclusion criteria, 85% (22/26), consented to participate. One child ($n = 1/22$) did not assent to participate in the DIS motor tasks and therefore dropped out from the study. For study inclusion, see Fig. 1. Neonatal patient characteristics are provided in Supplementary Table I.

2.1. Motor outcome

2.1.1. Phenotypic assessment

Three independent pediatric neurologists assessed the motor phenotype in a standardized way (using three main categories: normal, abnormal (CP), suboptimal/developmental; see Appendix B). Patients were assigned to a phenotype, when at least 2 of 3

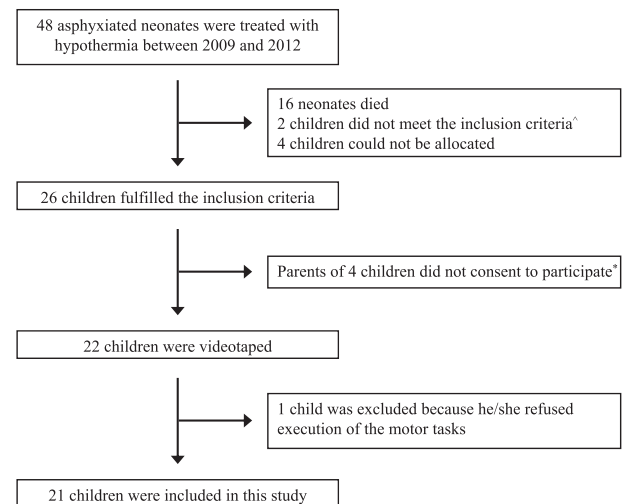


Fig. 1. Study inclusion. Flowchart of study inclusion. * 2 children were excluded because of shoulder dystocia ($n = 1$) and velo-cardio-facial syndrome (22q.11.2 syndrome); *1 of 4 children whose parents did not consent to participate was clinically diagnosed with dyskinetic cerebral palsy.

pediatric neurologists indicated the same phenotype. We determined the phenotypic agreement between the pediatric neurologists.

2.1.2. Quantification of dyskinetic CP features

The DIS is a recently developed rating scale for children with dyskinetic CP, consisting of the summed dystonia (DIS-D) and choreoathetosis (DIS-C) subscales. (9) Both subscales quantify the duration and amplitude of dystonia and choreo-athetosis in 12 body regions, including the eyes, mouth, neck, trunk, proximal and distal limbs on each side [10]. Seven different, independent, trained investigators in pediatric movement disorders quantified the videotaped motor performances, exactly according to the DIS guidelines [10]. We determined the mean scores and the inter-observer agreement between the observers. The assessors were not informed about the phenotypic assessments by the pediatric neurologists.

We determined inter-observer agreement of DIS (sub)scores. The mean DIS-scores from the present study were subsequently compared with previously reported: 1. age-related physiological DIS-scores in 52 healthy children [1], and 2. pathological DIS-scores in 55 children with dyskinetic CP [9]. In the referred dyskinetic CP group by Monbaliu et al. ($n = 55$), the reported distribution of Gross Motor Function Classification System (GMFCS) levels was: level I ($n = 10$), level II ($n = 5$), level III ($n = 6$), level IV ($n = 7$), level V ($n = 27$) [9].

2.2. Developmental outcome parameters

Parents of all included children completed a questionnaire concerning neurologic, cognitive and/or behavioral functioning, inter-current medical problems and prescribed medication (Appendix C). The questionnaire also included information on (pre-)school performances, to check whether the parental reports on cognition and/or behavior were consistent with the observations at (pre-)school. This appeared to be the case.

2.3. Retrospective neonatal parameters

2.3.1. Asphyxia parameters

We associated motor outcomes with the retrospectively collected neonatal asphyxia parameters, including: Apgar scores at

1, 5 and 10 min, umbilical artery pH and Thompson scores. In accordance with literature, we used the following asphyxia cut-off values: Apgar scores ≤ 3 [14]; umbilical artery pH < 7.0 [15]; Thompson score ≥ 11 [16]). We associated the neonatal asphyxia parameters with the motor phenotypes and DIS-scores by calculating the predictive value.

2.3.2. MRI parameters

A specialized pediatric neuro-radiologist (LM) performed blinded assessment of the neonatal MRI scans (conventional and diffusion weighted imaging), in accordance with a standardized protocol (Appendix D) [17]. Scored abnormalities were: 1. Cerebral cortical edema and high signal in basal ganglia, thalami, corpus callosum and cerebellum on axial T2 weighted images, decreased or lost high signal in the PLIC on inversion recovery (IR), hippocampal edema on coronal T2 weighted images, punctate white matter lesions (PWML) on sagittal T1 weighted images, 2. Diffusion restriction in the same areas as described in 1.

2.3.3. aEEG and EEG parameters

We analyzed neonatal aEEG recordings during TH treatment at 12, 24 and 48 h and after re-warming. We assessed the aEEG recordings by pattern recognition. All traces were assessed by one senior neonatologist (HtH) blinded to the severity of the HIE. The aEEG background patterns, epileptic activity (EA), and the presence of sleep-wake cycling (SWC) were assessed. We classified the various aEEG background patterns as continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), continuous low voltage (CLV), or flat trace (FT), according to the criteria established by Toet et al. [18]. We considered CNV to be a normal background pattern and DNV as mildly abnormal. The low voltage traces, BS, CLV, and FT, were considered as severely abnormal.

Neonatal EEGs were performed after re-warming at a median age of 5 postnatal days (range 1–19 days). We assessed neonatal EEG outcomes for: background activity (continuous/discontinuous), frequency, voltage, reactivity and epileptiform activity. We calculated the predictive value of these neonatal EEG parameters for the observed motor phenotypes and DIS-scores. We classified epileptiform activity as: 1. a single seizure in case of a single event of sudden, sustained high cortical activity, 2. repetitive seizures in case of repetitive events of sudden, sustained high cortical activity, and 3. status epilepticus in case of repeated epileptic activity resulting in a regular pattern of increased cortical activity (saw-tooth pattern) lasting for more than 50% of a 1 h period.

2.4. Statistical analyses

We performed statistical analyses using PASW Statistics 20 for Windows (SPSS Inc, Chicago IL, USA). In the included children, there were no missing parameters. We determined inter-observer agreement for the phenotype by Gwet's Agreement Coefficient (AC_1) and interpreted outcomes by criteria of Landis and Koch: $AC_1 < 0.20$: slight; 0.21 to 0.40: fair; 0.41 to 0.60: moderate; 0.61 to 0.80: substantial; > 0.81 : almost perfect [19]. We determined inter-observer agreement by the Intraclass Correlation Coefficient (ICC), using the two-way mixed model and single measurement coefficients. For uniformity, we also interpreted ICC outcomes by criteria of Landis and Koch [19]. We assessed normality of the distribution of the DIS-scores, both graphically and with the Shapiro-Wilk test. We compared DIS, DIS-D and DIS-C outcomes with healthy age-matched controls and with dyskinetic CP children using the unpaired *t*-test or, when outcomes were not normally distributed, using the Mann Whitney *U* test. To determine the influence of age on the DIS-scores, we performed a linear regression

analysis on the influence of age on DIS outcomes. For the association between asphyxia severity, neonatal MRI- and EEG-parameters and motor outcome, we calculated the predictive value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) per parameter for the motor phenotype. For the influences of these parameters on the DIS-scores, we performed a multivariable regression analysis with a forward stepwise model with age as the first fixed variable. All statistical tests were two-sided. *P*-values of $< .05$ (two-sided) were considered to indicate statistical significance.

3. Results

3.1. Motor phenotypes and DIS-scores at pre-school age

Inter-observer agreement on phenotypic assessment was significant ($p < .05$) [Gwet's AC_1 : 0.80 for spasticity ("almost perfect"), 0.66 for dystonia ("moderate"), 0.80 for mild coordination impairment ("almost perfect") and 0.72 for normal ("substantial")]. Inter-observer agreement on DIS-scores was significant ($p < .001$) for: DIS total (ICC = 0.31); "fair" and DIS-D (ICC = 0.43; "moderate"). Mean DIS, DIS-D and DIS-C scores were not normally distributed ($p < .01$).

At pre-school age, the motor phenotype of the included children was indicated as: 1. "normal" in 18/21 (86%), 2. "mildly impaired due to insufficient coordination, but in absence of phenotypic CP" in 2/21 (14%; case 1 and 14; indicated by 2/3 assessors), and 3. "abnormal" due to "dyskinetic CP" in 1/21 (7%; GMFCS level 2 with spastic, dystonic and choreatic features; indicated by all 3/3 assessors). In the child with dyskinetic CP, DIS-scores corresponded with the previously published score-range for patients with dyskinetic CP [9]. The DIS-scores of the two children with a mildly impaired phenotype (due to mildly impaired coordination) were in the same range as the 18 other children with a normal phenotype, see Fig. 2. In the 20 children without CP (i.e. normal and mildly abnormal phenotypes, $n = 20/21$), DIS-total, DIS-dystonia and DIS-chorea (DIS, DIS-D and DIS-C) subscores were significantly lower (better) than in patients with dyskinetic CP (mean difference: 71, 55 and 16 points, for DIS, DIS-D and DIS-C scores respectively; all $p < .05$) [9]. However, DIS, DIS-D and DIS-C scores were simultaneously also significantly higher than in healthy age-matched control children (mean difference: 14, 5 and 11 points, for DIS-T, DIS-D and DIS-C scores respectively; all $p < .05$) [1]. Scores are shown in Fig. 2 and Supplementary Table II. Analogous to healthy control children, TH-HIE treated children without CP ($n = 20/21$), revealed a significant association between mean DIS and DIS-D scores and age (months) (DIS: $B = -0.29$, $p = .044$; DIS-D: $B = -0.24$, $p = .024$).

3.2. Neurodevelopmental outcome parameters

At 3–6 years of age, the child with dyskinetic CP revealed impaired cognition (BSID-III cognition: 70). This child attended a school for children with special needs. The two children with mild coordination impairment revealed some attention deficits ($n = 1/2$) and/or language impairment ($n = 2/2$), but no cognitive impairment. The 18 children with a normal motor phenotype revealed no cognitive and/or behavioral problems, except for one child with social emotional problems. None of the children developed epilepsy. Cognitive and behavioral problems were statistically associated with DIS-D scores ($B = 18.3$; $p = .046$), see Table 1. For an overview of neurological outcome parameters, see Tables 1 and 2.

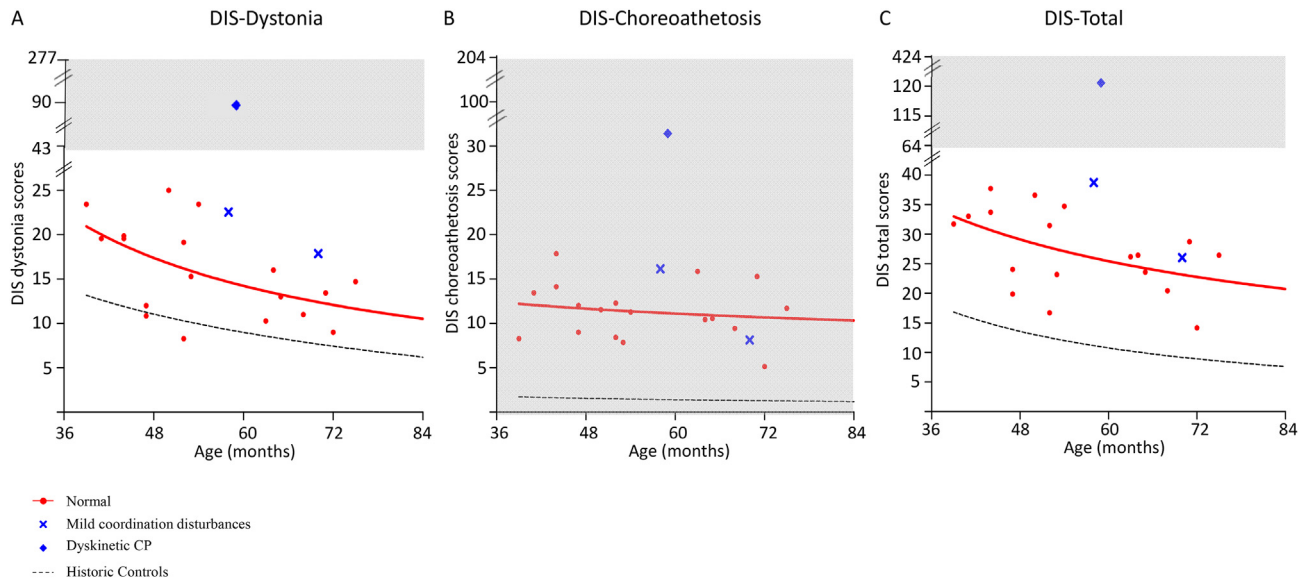


Fig. 2. DIS outcomes in relation to age. DIS-Dystonia (A), DIS-Choreoathetosis (B) and DIS-Total (C) scores in relation to age. Data points represent mean scores per child. normal = DIS score in TH-HIE treated children with a normal phenotype; mild coordination disturbances = DIS scores in children with a mildly impaired phenotype due to insufficient coordination; dyskinetic CP = DIS scores in a child with dyskinetic CP. Lines concern a best fitting trend line for continuous scales. The dotted line represents the DIS scores in healthy, age-matched controls (aged 3–6 years of age; $p < .05$), obtained from Kuiper et al. [1]. The red line represents the DIS scores in TH-HIE treated children with a normal phenotypic outcome. The grey areas represent the ranges of DIS scores in dyskinetic CP patients ($n = 55$; 6–22 years of age, mean 14.5 years of age), calculated as absolute values [9]. Total DIS score: median = 286 score; range: 64–424 (interquartile range: 206–340); DIS Dystonia score: median = 202; range 43–277 (interquartile range: 150–233); DIS Choreoathetosis score: median = 77; range: 0–204 (interquartile range: 42–118), previously published by Ref. [9]. Despite the younger age-range of the presently studied TH-HIE group (3–6 years of age) than that of the children with dyskinetic CP (6–22 years of age), all TH-HIE DIS scores were significantly higher than in healthy age-matched controls and significantly lower than previously obtained in children with dyskinetic CP; all $p < .05$.

Table 1
Predictors of phenotypic and quantitative motor outcome.

	Abnormal motor phenotype				DIS	DIS-D	DIS-C
	Sensitivity	Specificity	PPV	NPV	B (SE)	B (SE)	B (SE)
Neurological outcome							
Cognitive or behavioral problems	100%	94%	75%	100%	22.8 (11)	18.3 (8.6)*	4.5 (2.9)
Epilepsy	0%	100%	—	86%	—	—	—
Asphyxia severity parameters [§]							
Apgar score at 1 min ⁺	100%	17%	17%	100%	−1.9 (3.6)	−1.5 (2.8)	−0.4 (0.9)
Apgar score at 5 min ⁺	67%	50%	18%	90%	−2.1 (2.8)	−2.0 (2.2)	−0.0 (0.7)
Apgar score at 10 min ⁺	33%	87%	33%	87%	−3.5 (3.1)	−2.9 (2.4)	−0.6 (0.8)
Umbilical cord pH [#]	67%	50%	25%	86%	−16.9 (47.2)	−20.9 (36.7)	4.0 (11.3)
Thompson score ⁺	33%	82%	33%	82%	−2.0 (3.1)	−1.3 (2.4)	−0.7 (0.7)
Neonatal MRI							
Cortical abnormalities (conventional & DWI)	67%	100%	100%	95%	0.1 (8.1)	0.3 (6.4)	−0.1 (2.0)
Cerebellar abnormalities (conventional & DWI)	33%	100%	100%	90%	7.0 (22.4)	3.0 (17.5)	3.9 (5.6)
PLIC abnormalities (conventional)	67%	50%	18%	90%	−10.9 (7.2)	−8.4 (5.6)	−2.5 (1.8)
BGT abnormalities (DWI)	33%	100%	100%	90%	46.5 (3.6)**	36.5 (2.7)**	10.0 (1.7)**
EEG							
Discontinuous background pattern	67%	93%	67%	93%	29.7 (13.5)*	24.4 (10.3)*	5.3 (3.7)
Epileptiform activity	100%	36%	25%	100%	9.8 (5.6)	7.7 (4.3)	2.1 (1.5)
Neonatal convulsions	100%	56%	27%	100%	15.0 (8.9)	11.9 (7.0)	3.1 (2.3)

Legends. For motor phenotype, we calculated the sensitivity, specificity, PPV and NPV per neurological, asphyxia severity parameters and MRI and EEG abnormalities.

[§] For the calculation of sensitivity, specificity, PPV and NPV for motor phenotype, we categorized the asphyxia severity parameters: +Apgar score between 0 and 3(18); # Umbilical cord pH < 7.0(19); + Thompson score ≤ 11(20); For DIS scores, we calculated the regression coefficients; PPV = positive predictive value; NPV = negative predictive value; B = regression coefficient; SE = standard error; * $p < .05$; ** $p < .001$.

3.3. Retrospective neonatal parameters

For perinatal asphyxia parameters, see [supplementary Table I](#). Neonatal cerebral MRIs were performed in all included children ($n = 21$), at a median age of 6 postnatal days (range 3–38 days). For conventional and diffusion-weighted imaging MRI assessment, see [supplementary Tables III and IV](#). Neonatal aEEG parameters (at 12 and 48 h after cooling and 24 h after warming) are indicated in

[supplementary Table V](#). Neonatal EEGs were performed in 17 of the 21 infants (81%), at a median age of 5 postnatal days (range 1–19 days). Neonatal EEGs revealed discontinuous background activity ($n = 3/17$; 18%) and/or epileptiform activity ($n = 12/17$; 71%), see [supplementary Table VI](#). Clinical neonatal seizures were reported in 9/21 (43%) patients at a median age of 2 postnatal days (range: 1 h – 9 postnatal days).

Table 2
Motor outcome, neurologic outcome and neonatal parameters (MRI, EEG).

Pt#	Motor outcome	DIS score	Neurological outcome	Conventional MRI ⁺	DWI MRI ⁺	EEG background*
1	Ataxia	26	Attention deficit	Cortex, PLIC bi [†]	Cortex	D
7	Spasticity, Dystonia	121	Impaired cognition	—	BGT, Cortex	D
14	Ataxia	39	Specific language impairment	Cortex, Cerebellum	Cortex, Cerebellum	C
17	Normal	17	Social emotional problem	PLIC bi [‡]	—	C

Legends. DIS = Dyskinesia Impairment Scale (total score); MRI = Magnetic Resonance Imaging; DWI = Diffusion-Weighted Imaging; EEG = Electroencephalogram; ⁺location of damage; PLIC (bi) = Posterior Limb Internal Capsule (bilateral); [†]Equivocal (small) PLIC abnormality; [‡]Absent PLIC; [BGT] = Basal Ganglia and Thalamus; * EEG background pattern: [D] = discontinuous; [C] = continuous.

3.4. Motor outcome (phenotype and DIS-scores) versus retrospective neonatal parameters

The one child with dyskinetic CP (GMFCS II) revealed an abnormal discontinuous neonatal aEEG at 48 h with repetitive epileptiform activity, an abnormal aEEG after warming (continuous low voltage), a discontinuous neonatal EEG and bilateral cortical and basal ganglia damage on DWI. Neonatal MRI damage at the basal ganglia and thalamus and an abnormal discontinuous neonatal EEG/aEEG background pattern were both associated with an abnormal motor phenotype (PPV: 100% and 67%, respectively). Neonatal MRI-DWI abnormalities at the basal ganglia and thalamus were the only MRI abnormalities which were linked with abnormal higher DIS, DIS-D and DIS-C scores (B = 46.5, B = 36.5 and B = 10.0, respectively (all $p < .001$)). An abnormal aEEG background pattern during cooling and a discontinuous neonatal EEG background pattern was associated with abnormal DIS and DIS-D scores ($p < .05$). Mildly impaired coordination (in absence of CP) was associated with neonatal cerebral (sub)cortical and cerebellar abnormalities. For an overview of motor- and neonatal asphyxia parameters, see [Tables 1 and 2](#)

4. Discussion

After TH-HIE treatment, 95% (20/21) of the investigated pre-school children revealed a favorable neurologic outcome, in absence of cerebral palsy and/or epilepsy. The DIS-scores were significantly lower (better) than in children with dyskinetic CP [9] and significantly higher than in age-matched controls [1].

4.1. Motor phenotypes and DIS-scores at pre-school age

In the TH-HIE treatment group, we observed a higher percentage of normal motor phenotypes ($n = 18/21$; $\approx 85\%$) than previously reported by others (41–68%), [20,21]. This difference cannot be attributed to the mortality rate, as the mortality rate was similar to the reported literature (33% versus 28–32%) [20,21]. Another explanation could be that the Dutch-Flemish inclusion criteria for TH-HIE treatment are relatively mild [13]. According to the Dutch-Flemish protocol for TH-HIE inclusion, children with a 5-min Apgar score ≤ 5 are eligible for TH treatment, whereas other centers include children with a 10-min Apgar score ≤ 5 [2,5,20]. Additionally, according to the Dutch-Flemish protocol, children with clinical signs of encephalopathy or abnormal aEEG parameters are eligible for TH treatment, whereas other protocols require the presence of *both* criteria [2,20]. This could theoretically result in the inclusion of relatively mildly affected neonates. Finally, in our study, eligible newborns were already passively being cooled in the resuscitation room, prior to the transport to our specialized neonatal care unit. Upon arrival, the mean body temperature before the initiation of TH-HIE treatment was 34.5° Celsius (standard deviation 1.3° Celsius). As we strictly followed the national Dutch-Flemish guidelines for TH-HIE inclusion, it is not discernible

whether we obtained favorable results by: the inclusion of relatively mild cases; a favorable effect by the Dutch-Flemish cooling protocol; the passive pre-cooling strategy; or by a combination of all factors.

Analogous to the favorable phenotypic motor outcomes, we also obtained clearly lower (more favorable) DIS-scores, than previously reported in children with dyskinetic CP [9]. However, the obtained DIS-scores were still higher (less favorable) than in age-matched healthy controls [1]. This implicates that previously treated TH-HIE children may still reveal a relative over-representation of dyskinetic motor features. For instance, such discrete dyskinetic features were observed around the mouth (dystonic), the eyes (choreoathetotic), distal arms and legs. Until now, it is unclear whether these features should be interpreted as imminent minor neurologic impairment, or as a reflection of (delayed) development of the motor network. Since we observed similar age-related DIS-score trends in TH-HIE treated children as in healthy controls [1], one could hypothesize that the DIS-scores in TH-HIE treated children may eventually reach healthy control values at a later time point. In the near future, we hope to elucidate this to further extent.

4.2. Neurodevelopmental outcome parameters

Correlating parentally reported cognitive and behavioral impairment with motor outcome (DIS-scores and motor phenotype), revealed a positive association. Although a direct relation with underlying cerebral damage appears likely [21], it is important to realize that the reported prevalence of cognitive and behavioral problems in our study group was low and only slightly higher than that of the average Dutch population (i.e. 15% versus 5–10%, resp.) [22]. Nevertheless, these results could be interpreted as supportive of the data by Perez et al. indicating that children who have sustained neonatal HIE without developing CP are still at risk for long-term neuro-developmental (IQ) deficits [23]. As the children from our study group are still young, we cannot exclude that they might experience cognitive and/or behavioral problems at an older age [24]. In the future, we aim to provide long term follow-up data including the results by neuro-psychological assessment.

4.3. Retrospective neonatal parameters

Analogous with other studies [25–28], we observed a retrospective association between combined neonatal parameters (aEEG, EEG, MRI (DWI)) and motor outcome parameters. Solitary MRI parameters for basal ganglia and thalamus injury were linked with the development of dyskinetic CP and pathologic DIS-scores [9]. Additionally, isolated MRI-DWI injury at the cerebral cortex and cerebellum seemed associated with mildly impaired motor coordination in two children. Analogous with the DIS-score profiles, we observed that the ataxia rating scale scores (SARA) in these two children were higher than the SARA-scores in age-matched controls [12], and clearly lower (more favorable) than the SARA-scores in children with early onset ataxia (data not shown) [29].

Previous studies have demonstrated that there is a relationship between hampered cerebellar growth and asphyxia [30]. In addition to cerebellar impairment [31], injury to the white matter [32] causing disturbed signaling within the cerebral motor network, could also induce suboptimal motor coordination. In literature, similar pathologic mechanisms have been proposed in children with developmental coordination disorder (DCD) [33–35]. In children with DCD, we have observed similarly increased SARA scores as in present study group [36]. However, although these similarities may suggest a common ground, this remains entirely speculative as the age of our study group was too young for consideration of the DCD diagnosis (i.e. < 5 years of age).

4.4. Limitations

We recognize several limitations to this study. First, the number of included children is relatively small. Second, the observed ICC values on DIS-scores in TH-HIE children were smaller than in children with dyskinetic CP (0.32–0.43 versus 0.91–0.98, respectively) [9]. However, the observed ICC values were significant and similar to previously reported values in healthy control children (0.23–0.46) [1]. As previously indicated [1], lower ICC values can also result from a low variance in scores. Children with a (nearly) normal motor phenotype and, consequently also a low variance in scores will mathematically obtain lower ICC values than children with a high variance in scores [12,37]. Third, we are aware that a prolonged follow-up period, additional Movement-ABC data and neuro-psychological testing will provide worthwhile information. In the future, we aim to obtain this information during follow-up. Fourth, the motor phenotypes were assessed from videotapes and we did not include additional neurologic parameters. Although we cannot exclude that this may have under-estimated the phenotypic results, we have no indications that this was the case (neither from the patient records, nor from the parental reports, general practitioners and/or school doctors surveillance). Finally, we have not been able to trace all patients for study inclusion. Nevertheless, non-inclusion was random and the presently investigated children revealed a similar CP percentage as anticipated from the available patient record data of the total group (5% versus 7%, respectively). We would therefore suggest that the presented data could be interpreted as representative.

5. Conclusion

Motor outcome was favorable in the vast majority of preschool children who received TH-HIE treatment according to the Dutch-Flemish protocol. However, the study group still revealed a higher prevalence of dyskinetic motor features than healthy, age-matched controls. Future long-term follow-up data may hopefully elucidate whether this implicates the development of minor neurological impairment, or not.

Disclosure of interest

The authors state that they had no interests which might be perceived as posing a conflict or bias.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2020.07.013>.

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